University of North Carolina at Chapel Hill

Consent for Genotype Screening With Identifying Information--PILOT STUDY 1

IRB Study # 07-0190 **GCRC #: 2579**
Consent Form Version Date: June 27, 2008

Title of Study: Cardioprotective Effects of Omega-3 Fatty Acids Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust
A Pilot Study to Identify the Optimum Diesel Exhaust Concentration to Investigate the Cardiovascular Effects in Healthy Older Subjects
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Co-PI: Robert Devlin, PhD.
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Faculty Advisor:
Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-0665 (James M Samet)
Study Contact email: samet.james@epa.gov

What are some general things you should know about this research study?
Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the

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researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
Recent reports have shown that people with a particular gene, known as the GSTM1 null gene, are more susceptible to air pollutants such as ozone and diesel exhaust. Another gene called GSTP1 gene is also associated with a significant risk to the effects of air pollutants. The purpose of this pilot study is to look at the cardiovascular and respiratory effects of diesel exhaust in older subjects who do not carry GSTM1 and have different GSTP1 genotypes (Ile/Ile, Ile/Val, and Val/Val). The purpose of this screening session is to determine whether you carry a GSTM1 gene and your GSTP1 genotypes in order for us to make selection.

How many subjects will participate in this study?
If you decide to participate, you will be one of approximately 6 participants who will complete in this pilot study.

How long will your participation last?
Participation in this genetic screening session of the study will last for approximately 30 minutes.

What will happen if you participate in this study?
We will briefly review your medical history and any medical conditions that you have or medications that you are currently taking. You will sign 2 copies of the study consent form. We will measure your blood pressure and draw about 50 ml of blood for genotyping and blood analysis. If you are re-contacted from the previous study, you will not need genotype screening but you will need to get blood drawn for other blood analysis. At the end, we will give you a copy of the Medical History Form and please hold the form until you hear from us that you are qualified for the study, and then fill it out and mail it back to the Westat recruitment office.

How will the blood sample be collected?
You will have about 50 ml (about 3 1/3 tablespoon) of blood taken by our trained nursing staff.

What will happen to the blood?
The blood sample collected will be used to look at the GSTM1 gene and GSTP1 genotypes. If there are excess samples left over after use for the purposes of this specific study, they will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill North Carolina. Only project members of the study will have access to the samples.

During the course of this research, other researchers may request access to specimens for as-of-yet unspecified research that may or may not be related to the original research from which the specimens were derived. In these cases, provided appropriate IRB approved consent has been obtained from subjects, these specimens will be provided without identifiers to these other researchers by employing a data use agreement.

Are there any reasons you should not participate?

- You should not participate in this portion of the study if you are not a candidate for the subsequent portions. The inclusion and exclusion criteria will be described. Briefly, you

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should not have chronic diseases including active allergies, lung diseases, diabetes, need for a heart pacemaker, a previous chest pain and heart attack or coronary bypass surgery and uncontrolled high blood pressure. You are currently taking β-blockers. You are currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5 pack year smoking history. The investigators and medical staff will explain other potential exclusionary conditions in detail to you.

What are the possible benefits to you?

There are no direct benefits to you for completing this portion of the study. However, you will know your blood cholesterol levels and you will know your genotype of GSTM1 and GSTP1 genes and this information will determine if you will be qualified for the further diesel exposure study.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following minimal risks and/or discomforts to you:

1. The risks associated with taking blood samples are considered minimal. A well-trained member of the staff will draw the blood. Drawing blood could cause some bruising or minor pain, which usually resolves quickly. Also, a rare complication is skin infection or an infection of the vein in which the blood has been drawn. The risk of getting and infection is minimized by the use of sterile technique. If you do have signs of infection ant the site (redness, warmth, painful skin, and swelling) after completion of the procedure, you will need to contact the EPA medical station.

2. Risk of breach of confidentiality is minimal. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers

Will there be any cost to you to participate?

The U.S. EPA will pay the costs of this research. You will not be billed for any procedures.

Will you receive anything for being in this study?

You will be paid $30 for completing this screening procedure. We will give you parking coupons to cover the cost of parking. If you live more than 30 miles outside of the Chapel Hill/Carrboro area, you will be reimbursed for mileage at the current government rate. Money received by participants in research studies is normally treated as ordinary income by taxing authorities and we will report payments made to you to the Internal Revenue Service as required by law.

Who owns the blood samples?

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Any blood samples obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?

You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records which use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Samples used for genetic analysis will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

Will researchers seek approval from you to do future studies involving the blood samples?

By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive study results of future research involving your blood samples?

Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Can you withdraw the blood samples from the research study?

If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board,

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University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury form having your specimen collected. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. **Neither the University of North Carolina at Chapel Hill nor the U.S. EPA has set aside funds to pay you for any such reactions or injuries, or for the related medical care.** If you believe that you have suffered a research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research-related injury occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

Who is sponsoring this study?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?

All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

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Title of Study: Cardioprotective Effects of Omega-3 Fatty Acids Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust

A Pilot Study to Identify the Optimum Diesel Exhaust Concentration to Investigate the Cardiovascular Effects in Healthy Older Subjects

Principal Investigator: Haiyan Tong, MD, PhD; James M Samet, PhD

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

Initial/Date _____

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 7/3/08 AND 2/9/09
APPROVED BY
INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects

Biomedical Form—PILOT STUDY 3

IRB Study #__07-0190_____ GCRC #: 2579
Consent Form Version Date: June 27, 2008

Title of Study: Cardioprotective Effects of Omega-3 Fatty Acid Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust

A Pilot Study to Identify the Optimum Diesel Exhaust Concentration to Investigate the Cardiovascular Effects in Healthy Older Subjects

Principal Investigator: Haiyan Tong, MD, PhD; James M Samet, PhD, MPH;
Co-PI: Robert Devlin, PhD.
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Email Address: tong.haiyan@epa.gov, samet.james@epa.gov
Co-Investigators: Martha Almond RRT; Maryann Bassett, RN; Philip Bromberg, MD; Martha Sue Carraway, MD; Martin Case, BS; Wayne Cascio, MD; Melissa Caughey, BS, RVT; David DeMarini, PhD; Andrew Ghio MD; Milan Hazucha, MD, PhD; Alan Hinderliter, MD; Fernando Holguin, MD; Debbie Levin, BSN; Margaret Herbst, RN, MSN; Sally Ivins, BA; Howard Kehrl, MD; Tracey Montilla, RN; Lynne Newlin-Clapp, BA; Dave Peden, MD, MS; Carole Robinette, MS; Michael Schmitt, MS; and Susan Steck, PhD, RD; Haibo Zhou, PhD.
Faculty Advisor:
Funding Source: US Environmental Protection Agency Intramural Federal Research

Study Contact telephone number: (919) 966-0665 (James M Samet)
Study Contact email: samet.james@epa.gov

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason at any time.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Your participation is voluntary. Deciding not to be in the study or leaving the study before it is completed will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

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Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The main purpose of this pilot study is to identify an optimal concentration of diesel exhaust which can be used to study the risks of cardiac changes in healthy older subjects. Results from this study may increase the understanding of how gaseous and particulate air pollutants (which causes the haze seen in some polluted cities) may adversely affect the functioning of the human cardiovascular (heart and blood vessels) and respiratory (lungs) systems. This understanding may be especially important for patients with cardiopulmonary diseases.

You are being asked to be in this pilot study because:

- You are 50-75 years old, generally healthy.
- You have a normal resting electrocardiogram (ECG).
- Your oxygen saturation is greater than 94% at the time of physical exam.

Are there any reasons you should not be in this study?

You should not participate in this pilot study if…

- You have a history of chest pain, irregular heart beats, and heart attack or coronary bypass surgery.
- You have a heart pacemaker.
- You have untreated high blood pressure (> 150 systolic, > 90 diastolic).
- You have a history of lung disease and/or active allergy including: hay fever, dust allergies, rhinitis, asthma, chronic bronchitis, chronic obstructive pulmonary disease, tuberculosis, coughing up blood, recurrent pneumonia, chronic or allergic rhinitis or acute or chronic sinusitis.
- You are currently taking β-blockers (such as atenolol, metoprolol, propanolol, and acebutolol).
- You have a history of bleeding or coagulation disorders and are taking blood thinner medication.
- You are currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5 pack year smoking history.
- You are a diabetic.
- You have cancer.
- You are currently taking estrogen replacement therapy.
- You are pregnant, attempting to become pregnant or breastfeeding.
- You have an allergy to latex.

You should **NOT** participate if you are unable to comply with the following requirements:

- No omega-3 fatty acids or having more than one 4-6 oz/serving of all types of fish and shellfish, walnuts, flaxseeds and flaxseed oil, rapeseed oil, canola oil, soybeans and soy products, Eggland's Best eggs, and cod liver oil for two weeks before the exposure.

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- No antioxidants (eg, beta-carotene, selenium, vitamin C, vitamin E, zinc) for two weeks before the exposure.
- No over-the-counter pain medications such as aspirin, Advil, Aleve or other non-steroidal anti-inflammatory medications for 2 weeks prior to the exposure and post-exposure visits. Low-dose aspirin and Tylenol (acetaminophen) are permitted.
- Avoid smoke and fumes for 24 hours before all visits.
- Avoid drinking alcohol 24 hours before all visits.
- Avoid strenuous exercise for 24 hours prior to and after all visits.
- Eat a light breakfast on the exposure day.
- Not eat pan fried and/or grilled foods after midnight prior to the exposure day.
- Not consume caffeine for 12 hours prior to the exposure and post-exposure visits.

How many people will take part in this study?
If you decide to be in this study, you will be one of approximately 6 people who will complete this pilot research study.

How long will your participation in this study last?
You will have up to 7 visits to the research facility over approximately 18-20 weeks if you are eligible for the study (see attached pilot study design flow chart).

Your participation in this pilot study will include one training session (today) for about 3 hours, 3 exposure sessions each of which will last approximately 8 hours, and another 3 sessions which will occur 18 hours after each exposure and last approximately 3 hours.

Storage of some of your blood samples in this study may be indefinite.

What will happen if you take part in the study?
You should have already undergone a genetic screening visit and a general physical examination to ensure that you are a candidate for this study. If you are a female participating in this study, you should have been asked about your menstrual history. You will have a pregnancy test today and you will have another pregnancy test on exposure day if it is more than 7 days since today's pregnancy test.

Today's visit is expected to last about 3 hours. We will review the inclusion and exclusion criteria and any medical conditions that you have or medications that you are currently taking. We will go over the study in detail so that you will know what we will expect from you as a participant and what you should expect from us as investigators. If you agree to participate in the study you will sign 2 copies of the study consent form and we will give one copy to you.

We will then train you on a breathing instrument to prepare you for your exposure session. This is known as spirometry, and you will breathe through a filter into the instrument. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.

We will collect your baseline heart rate viability (HRV) by a Holter monitor. You will have several ECG leads attached to your chest. It may be necessary to clean and shave the areas of

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your chest where these leads will be placed. The leads will be connected to a monitor (small recording devices about the size and weight of a portable tape player) to obtain readings of your heart rate and rhythm. The monitor will be kept on you for about 24 hours until you return the next day to get the monitor removed.

After these tests have been successfully performed, and if you are deemed to be a suitable candidate and you decide to participate in this study, you will be scheduled for your first exposure at diesel exhaust concentration of approximately 100 $\mu g/m^3$ for 2 hours in a small exposure chamber. About 2 weeks later you will have another diesel exposure at approximately 200 $\mu g/m^3$ for 2 hours. We will analyze the results after everyone finishing the 200 $\mu g/m^3$ exposure and decide whether we will continue on the 300 $\mu g/m^3$ exposure. If we decided to continue, you will have the third exposure at approximately 300 $\mu g/m^3$ for 2 hours that will occur about 2 weeks later. You may terminate your participation from this study at any time. Our goal of this pilot study is to find an optimal concentration of diesel exhaust to be used in a future study. You may not have all these 3 exposures if we determine to terminate this pilot study at some point based on interim results. In this pilot study, you will be monitored for symptoms that you may develop during the exposure and over the following 24 hour period. The symptoms include chest pain, difficult to breathe, light-headness, pale skin color, unstable step, and significant irregular heart beats. In addition, analyses of blood samples taken after exposure will be monitored for abnormalities, including elevated lactate level, changes in fibrinogen concentrations, as well as significant increases in inflammatory markers such as neutrophil counts and the concentration of c-reactive protein. The study physicians will stop the study if symptoms and/or changes detected in the blood samples that are considered clinically significant.

Exposure day

We will call you a few days before the exposure session to remind you of your scheduled visit. We will also remind you to refrain from alcohol, excessive amounts of caffeine, and from any activities where you could be exposed to high levels of pollutants (e.g., cigarette smoke, paint fumes) for a couple of days before your visit. Please report any pollutant exposure to the study personnel so you can be rescheduled if necessary. You will be rescheduled if you have experienced a respiratory tract illness within the past 4 weeks or any other illness within the past week. You should not eat pan fried or grilled meat before midnight of the exposure day (we will provide you with nutrition guidelines).

You will be asked to eat a light breakfast and arrive at the EPA medical station at approximately 8 am. You will need to wear comfortable clothes and shoes.

Prior to exposure, you will:

- Have your vital signs checked (heart rate, respiratory rate, blood pressure, oxygen saturation level, and a symptom questionnaire).
- Have your baseline heart rate viability (HRV) measured by a Holter monitor. You will have several ECG leads attached to your chest. It may be necessary to clean and shave the areas of your chest where these leads will be placed. Excessive deodorant, skin lotions, and body sprays may interfere with the function of some of these leads so we will ask you not apply these to your chest area on the day you report to the HSF. The leads will be connected to 2 monitors (small recording

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devices about the size and weight of a portable tape player) to obtain readings of your heart rate and rhythm. One of these monitors will be removed at the end of the day and the other monitor will be kept on you until you return the next day. You will be asked to recline quietly and breathe at a constant rate for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm. It is important that you do not fall asleep during this 30-minute period. The following morning during your next visit to the facility, there will be a 30 minute measurement of your heart rate and then the monitor will be removed. These monitors will allow us to determine if diesel exhaust causes small changes in the ability of your nervous system to regulate how your heart beats.

- Have about 50 ml blood drawn (about 3 1/3 tablespoons). We will test this blood to see if diesel exhaust affects the ability of your blood to clot correctly, or changes proteins on the surface of blood cells. **With your permission, we may also store some of your blood we obtained during the study for yet-to-be-determined tests in the future.**
- We will measure the pulse wave of your finger arteries by a non-invasive method Endo-PAT 2000 (called Endo-PAT). We will place two small PAT probes to both of your index fingers and a tourniquet on your arm, much like a cuff used to measure blood pressure. First, you will be asked to rest quietly for 10 minutes, and then we will obtain recordings for 5 minutes at rest. Then the blood pressure cuff on your arm will be inflated for 5 minutes in order to stop the flow of blood. You may feel sensations similar to those when your foot "goes to sleep", such as "pins and needles" and tingling. We will obtain 5 minutes recording during the blood pressure cuff inflated. Another 5 minutes recording will be obtained after the blood pressure cuff is released.
- We will then take you to the General Clinical Research Center (GCRC) of North Carolina Memorial Hospital (NCMH) where we will conduct an ultrasound of an artery in your arm. The ultrasound operator will scan your arm with probe and then place a tourniquet on your arm, much like a cuff used to measure blood pressure. Measurement of the size of the artery will be made four times. First, you will be asked to rest quietly for 15 minutes, and then the first 90 second scan will be performed. Then the blood pressure cuff on your arm will be inflated for 5 minutes in order to stop the flow of blood. You may feel sensations similar to those when your foot "goes to sleep", such as "pins and needles" and tingling. After the pressure is released, a second scan will be taken of the artery. You will rest quietly for another 10 minutes, and a third ultrasound scan will be taken at the end of this rest period. You will then be given a dose of nitroglycerin under your tongue. This drug takes effect very quickly and is sometimes associated with a short-lasting headache or dizziness. Three minutes later, the final ultrasound scan will be made. You will then be asked to rest quietly for 5 minutes so that the effects of the drug will wear off before you leave the laboratory.
- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- Have about 30 ml of urine sample.

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- You will then enter the exposure chamber and be exposed to diesel exhaust.

During the exposure, you will:

- Have an exposure to diesel exhaust at approximately 100 $\mu g/m^3$ for 2 hours in a small exposure chamber. About 2 weeks later you will have another diesel exposure at approximately 200 $\mu g/m^3$ for 2 hours. The third exposure at approximately 300 $\mu g/m^3$ for 2 hours will be about 2 weeks after the second exposure. This particle concentration is representative of diesel levels which you would inhale if you were occupationally exposed to diesel, such as being a truck driver, but less than sites in some mines that utilize diesel-generated power. You would also be exposed to a similar total amount over about 5 hr, 10 hr or 15 hr at a busy intersection in a polluted city (such as Los Angeles) where diesel concentrations have been measured at 22 $\mu g/m^3$.
- You will be occasionally asked to breathe into a mouthpiece so that your rate of breathing can be measured. A trained investigator will be seated outside the chamber to observe you at all times and a physician will be on site during the entire exposure session. During the exposure, your heart rhythm, blood pressure, and the amount of oxygen in your blood will be monitored. If it appears you are experiencing significant heart rhythm or breathing problems, or have headache, nausea or vomiting the exposure will be terminated immediately. In addition, you may elect to terminate the exposure at any time.

Immediately following the exposure, you will:

- Have your vital signs checked.
- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- You will recline quietly for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm.
- We may obtain another Endo-PAT measurement.
- Have blood drawn (about 50 ml or about 3 1/3 tablespoons).
- Have about 30 ml of urine sample.
- Fill out a symptom score questionnaire.
- Have another arm artery ultrasound at GCRC.
- Be assessed and discharged by the nursing staff.

Importantly, because you will be asked to wear the portable ECG monitor attached to your chest until you return the next morning, for your safety you should not shower or bathe until after the monitor is removed.

Eighteen hour follow up visit (about 3 hours)
You will return to the HSF the next morning (approximately 18 hours after exposure) and you will:

- Have your vital signs checked.

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- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- You will recline quietly for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm.
- You might have another Endo-PAT measurement.
- Have blood drawn (about 50 ml or about 3 1/3 tablespoons).
- Fill out a symptom score questionnaire.
- Have the Holter monitor removed.

If there are any samples left over after all study information is collected, we will continue to store the samples for as yet undesignated studies. This allows us to make the best use of the samples we collect from subjects. You will be given a separate consent form for this storage, and you do not have to allow your samples to be stored indefinitely in order to participate in this study.

What are the possible benefits from being in this study?

You will not benefit directly from being in this research study, though by participating in this study you will receive a medical examination that includes blood work, respiratory test, and ECG monitoring of heart at no charge. However, this is not a substitute for a routine doctor visit. The medical staff will explain to you any remarkable findings regarding your overall health status. In addition, if we observe changes in your health status as a consequence of exposure to air pollutants, you may elect to use this information to avoid exposure on high pollution days.

This research is designed to benefit society by gaining new knowledge. Given that every member of American society is currently exposed to these pollutants, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these pollutants.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you:
If you have any tendency to become uncomfortable in small closed spaces, it is possible that you may become uncomfortable during this study. You will be taken to the exposure chamber when you are first evaluated for suitability for the study to allow you an opportunity to see where you will sit and what the chamber looks like.

Diesel exhaust exposure: Exposure to air pollution particles can cause cough, shortness of breath, chest discomfort, eye irritation, and headache. These symptoms typically last no more than a few hours, but could last longer if you are especially sensitive. You will wear protective goggles during the exposure time to reduce the eye irritation. There is a chance that exposure to particles can increase the likelihood that you will be more likely to come down with a respiratory infection within several days of the exposure. Diesel exhaust, even when diluted in this study, may have an unpleasant odor. Exposure to the air pollution particle concentrations used in this study for short periods of time has never been found to cause permanent health effects. However, some studies suggest that older people, particularly those with underlying cardiovascular

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diseases, are at increased risk for getting sick and even dying during episodes of high air pollution. At this time, no one understands exactly how these particles might cause people to become sick or die. While we can not exclude the possibility that you may have an adverse reaction to breathing theses exhausts, you will only be exposed to them for 2 hours, and you will not be exposed to more particles than you would be exposed to if you visited a large city such Los Angeles, New York, or Mexico City on a smoggy day.

You will be monitored continuously during the exposure session through a window in the chamber or by closed-circuit television, and can communicate with a staff member via an intercom. Your heart rate and rhythm will also be constantly monitored for any adverse changes brought about by the exposure. A licensed physician is always on the premises during exposures, and is available to respond in an emergency.

Heart rhythm monitoring: There is little risk associated with monitoring your heart by ECG or blood oxygen by pulse oximetry. However, preparing your skin for placement of ECG electrodes and removing the electrodes the next day may cause some irritation or skin discoloration, itching, or burning in some people. If this occurs you should call the nursing staff.

Venous blood sampling: The risks associated with taking blood samples are considered minimal. A well-trained member of the staff will draw the blood. Drawing blood could cause some bruising or minor pain, which usually resolves quickly. Also, a rare complication is skin infection or an infection of the vein in which the blood has been drawn. The risk of getting infection is minimized by the use of sterile technique. If you do have signs of infection at the site (redness, warmth, painful skin, and swelling) after completion of the procedure, you will need to contact the EPA medical station.

Brachial artery ultrasound (BAU) and Finger Endo-PAT: There are no significant risks associated with imaging of the finger arteries, or with brief episodes of forearm ischemia (reduced blood flow). Occlusion of blood flow to the arm may result in mild discomfort or temporary sensations of tingling or numbness until the blood pressure cuff is released. A small number of patients (about 1 in 200) develop a painless rash on the arm where the blood pressure cuff is placed; this disappears over several days. Some risks and discomforts may be unforeseeable. Sublingual nitroglycerin is a potent vasodilator, and may be associated with headache, flushing and transient lowering of your blood pressure. Since this drug is short-acting, however, these effects do not last long. To minimize the risk of low blood pressure, you will remain lying down for ten minutes after receiving nitroglycerin. As with any medication, nitroglycerin can cause an allergic reaction, such as a rash, in rare individuals. Some risks and discomforts may be unforeseeable.

Breathing tests (spirometry): You may cough or become dizzy during these tests. You will be seated in a chair, and if these symptoms occur, they are usually only temporary. You will be exposed to low dose of acetylene for a brief period of time (single breath in and breath out), thus the risk will be quite low.

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In addition, there may be uncommon or previously unrecognized risks that might occur. If you do notice any unusual symptoms occurring during the study you should call the EPA medical station or the on-call physician to report them.

What if we learn about new findings or information during the study?
You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will your privacy be protected?
You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records that use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Blood samples will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?
All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be required. In spite of all precautions, you might develop medical complications from participating in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company.

Neither the University of North Carolina at Chapel Hill nor the U.S. EPA has set aside funds to pay you for any such reactions or injuries, or for the related medical care. If you believe that you have suffered a research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents

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from liability for negligence. If a research-related injury occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?
You will be paid approximately $12 per hour for your participation in this study and the total compensation for completion of this study will be approximately $2053.

If you are unable to complete the study for voluntary reasons or failure to comply with eligibility requirements you will receive full compensation for your participation up to that point. If you are dismissed by the investigators after enrollment in the study but prior to completion for involuntary reasons you will be paid for the entire study, excluding completion bonus.

We anticipate performing several tests on you during the course of this study. However, circumstances beyond our control may arise (i.e, equipment failure) which may prevent us from performing a specific test on you. If we are unable to perform a specific test on you which is a primary endpoint for us, you will be compensated for all tests and time completed on that day and rescheduled. If this test is a secondary endpoint for us and is also a source of compensation, you will be paid for that test, but not rescheduled to make up the procedure.

In addition, you will be reimbursed for reasonable travel expenses and for parking costs while at the research facility. Money received by participants in research studies is normally treated as ordinary income by taxing authorities and we will report payments made to you to the Internal Revenue Service as required by law. Payments totaling more than $600 in a year from a single or multiple EPA studies will be reported to the IRS. This summary is to emphasize the importance of all the visits, and to signify the importance of your time and commitment to the research study. The following table details the expected compensation for completion of the entire study:

Pre-study qualifications	
Recruitment screening	$15
Physical exam	$15
Venipuncture (~50ml) (genotyping)	$30
Pre-study qualification total =	$60
Pre-exposure screening/training (3 hours)	
Time (3h @$12/h)	$36
Holter monitor	$100
Exposure sessions (8 hours)	
Venipuncture (~50ml, pre; 3@$ 30 each)	$90

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Holter monitor (3@$ 100 each)	$300
Urine sampling (~30 ml, pre, 3@$ 10 each)	$30
Chamber exposure (2 hours; 3@$ 72 each)	$216
Venipuncture (~50ml, post; 3@$ 30 each)	$90
Urine sampling (~30 ml, post, 3@$ 10 each)	$30
Finger Endo-PAT (6@$10 each)	$60
Brachial artery ultrasound (6@ $50 each)	$300
Time (3X8h @$12/h)	$288
On-time bonus (3@$25 each)	$75

Total for completion of exposure = $1479

18 hours after exposure (3 hour)

Venipuncture (~50ml; 3@$ 30 each)	$90
Time (3X3 hrs @$12/h)	$108
Finger Endo-PAT (3@$10 each)	$30

Day 3 total for completion of post-exposure = $228

Protocol Completion Bonus (3@$50 each) $150

Approximate TOTAL for completion of the study = $2053

Subjects will be provided a lunch by GCRC for the exposure day. If a subject is terminated from the study or chooses to withdraw he/she will be reimbursed for time and procedures completed up to that time point.

You should understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty. If you voluntarily elect to withdraw from the study at any time or you fail to maintain compliance with eligibility requirements, you will be paid for that portion of the study that has been completed. In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, you will be paid $12 per hour for the time scheduled and canceled, and 50% of the reimbursement amount for procedures that are canceled up to a total maximum of $100 for all procedures. You will be paid in full for any procedures that may have been started during the current visit. Cancellations could occur due to adverse weather conditions, equipment failure, and other unforeseen events. When feasible, canceled visits will be rescheduled.

The investigators also have the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or because the entire study has been stopped, or for some other reason. If you are dismissed by the investigators prior to completion, you will be paid for the entire study excluding the completion bonus.

Will it cost you anything to be in this study?

There will be no cost to you for participating in the study. However, if you are deemed not eligible to participate in the study for medical reasons, we may suggest that you seek follow-up

Initial/Date _____

care from your own health care provider for abnormalities discovered during the screening history, physical examination, or the study. **Such care is entirely at your own expense. EPA will not provide reimbursement for any follow-up care.**

All study procedures will be paid for by the study. We will give you parking coupons to cover the cost of parking. If you live beyond Chapel Hill/Carrboro you will be reimbursed for mileage at the US Government mileage rate in effect at the time.

<u>What if you are a UNC student?</u>
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

<u>What if you are a UNC employee?</u>
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

<u>Who is sponsoring this study?</u>
This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

<u>What if you have questions about this study?</u>
You have the right to ask, and have answered, any questions you may have about this research. If you have further questions regarding this study, you should call one of the listed investigators:
James Samet, PhD 919-966-0665 Robert Devlin, PhD 919-966-6255

If you feel a research-related injury has occurred, please contact the HSF medical station or one of the investigators listed above. In addition, you should contact the Human Studies Division Human Research Officer and Director of the National Health Effects and Environmental Research Laboratory Human Research Protocol Office at 919-966-6217.

<u>What if you have questions about your rights as a research subject?</u>
All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

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Initial/Date ______________

Title of Study: Cardioprotective Effects of Omega-3 Fatty Acids Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust

A Pilot Study to Identify the Optimum Diesel Exhaust Concentration to Investigate the Cardiovascular Effects in Healthy Older Subjects

Principal Investigator: Haiyan Tong, MD, PhD; James M Samet, PhD

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

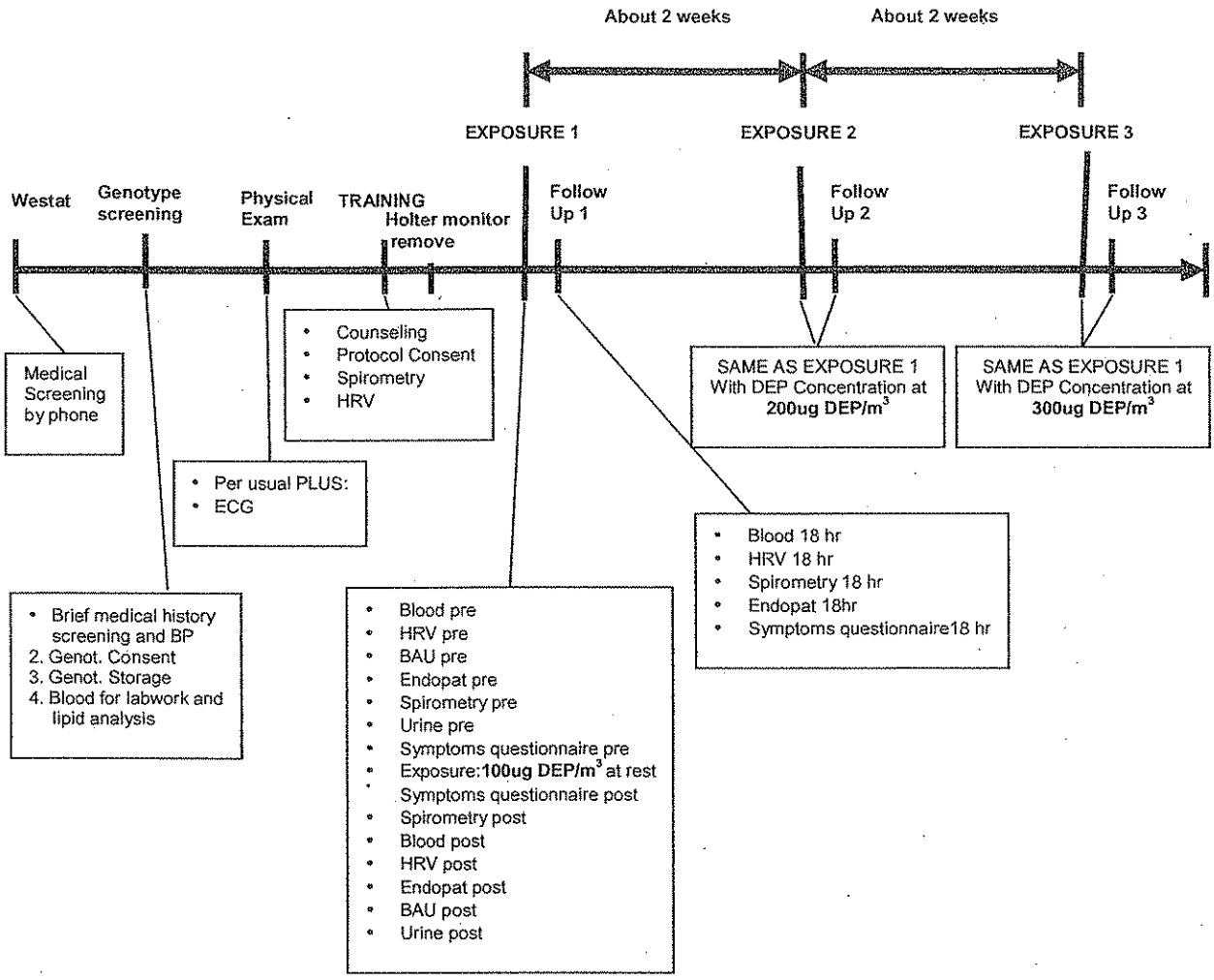
_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

Initial/Date _____



PILOT PHASE FLOW DIAGRAM

Initial/Date _____

First Review of IRB Submission Modification

Training Not Met (Haiyan Tong, Michael Schmitt, Tracey Montilla, David Demarini, Martin Case, Wayne Cascio, Mary Bassett)

Receipt Date : 7/03/2008 **Expiration Date :** 2/09/2009 **Previous Review Type:** **Renewal Full Board**

IRB: Biomedical **PI:** Haiyan Tong **IRB ID :** 07-0190 **IRB Coordinator :**

Title: GCRC-2579: Cardioprotective Effects of Omega-3 Fatty Acids Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust

☐ Not-HSR ☐ Exempt (Category:) ☑ Not Full IRB (Category:) ☐ Full IRB

Agenda Date Reviewer 1: Reviewer 2:

Entered by: Laura O Curry

Study Description:

The purpose of this study is to identify an optimal concentration of diesel exhaust which can be used to study the risks of cardiac changes in healthy older subjects. Healthy adults, ages 50 to 75 years, will complete seven visits over 18-20 weeks.

Submission Description:

PROCESSING STEPS (OFFICE USE ONLY):

☐ Reviewer Checklist completed
☐ Minor Stipulation letter:
- ☐ Draft letter prepared
- ☐ Approved by chair as attached (Initials/Date:)
- ☐ Approved by chair, see edits (Initials/Date:)
- ☐ Email copy sent
- ☐ Hard copy sent

☐ Approval letter:
- ☐ Draft letter prepared
- ☐ Approved by chair as attached (Initials/Date: 7/3/08)
- ☐ Approved by chair, see edits (Initials/Date:)
- ☐ Email copy sent
- ☐ Hard copy sent

Consent forms attached:
Other attachments:

FINAL ACTIONS:

☑ Approved
☐ Approved with Minor Stipulations
☐ NHSR
☐ Return to sender
☐ Termination

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board
MODIFICATION OF APPROVED
HUMAN SUBJECTS RESEARCH
version 29-Apr-2008b

Include the items indicated, where applicable:

- *Check* the relevant items below and include one copy of all checked items 1-5 in the order listed.
- Also include one additional collated set of copies (sorted in the order listed) for items 1 and 2.

→ **Applications will be returned if these instructions are not followed.**

Check	Item	Total No. of Copies
x	1. A concise summary of the requested modification using this form. List and describe each proposed change to aid in IRB review. Add pages as necessary. Provide a concise summary of changes when submitting an updated Investigator Brochure or Master Protocol.	2
x	2. New or revised consent forms, questionnaires, surveys, recruitment materials, advertisements, etc. One copy should have changes highlighted by underlining, and the other clean copy will be used for stamping.	1 highlighted 1 clean
□	3. If you have made substantive changes to the study design or procedures, submit a revised full IRB application with changes highlighted by underlining. If you are making changes only to the first page, just submit that page.	2
□	4. The sponsor's document describing the amendment, if any.	1
□	5. Only for those study personnel *not* in the online UNC-CH ethics training database (http://cfx3.research.unc.edu/training_comp/): Documentation of required training in human research ethics.	1

1 List and describe each proposed change:

Modify the exclusion criteria of subjects smoking history in the study. The changes are highlighted in the pilot consent and genotyping consent forms.

The new exclusion criteria for the smoking history defined as: subjects are currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5 pack year smoking history.

2. Is this modification being submitted in response to an unanticipated problem or adverse event? ___yes __x_no

3. Do any of the proposed changes increase risk? ___yes _x__no If yes, explain.

IRB study #: 07-0190 GCRC #: 2579 **Date: June 27, 2008**

Title of Study: Cardioprotective Effects of Omega-3 Fatty Acids Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust

Principal Investigator: Haiyan Tong, MD, PhD **Faculty advisor:** James M Samet, PhD (if applicable)

For industry sponsored research (if applicable):
Sponsor's master protocol version #: Version date:

Investigator Brochure version #:

Version date:

Any other details you need documented on IRB approval:

Signature of Principal Investigator or designee

6/27/08

Date

Signature of Faculty Advisor (if applicable)

Date

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

To: Haiyan Tong
Environmentally Protection Agency
CB# 7315

From: Biomedical IRB

Authorized signature on behalf of IRB

Approval Date: 7/11/2008
Expiration Date of Approval: 2/09/2009

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Reviewed Research
Study #: 07-0190
Other #: GCRC : 2579
Study Title: GCRC-2579: Cardioprotective Effects of Omega-3 Fatty Acids Supplementation in Healthy Older Subjects Exposed to Diesel Exhaust
Sponsors: EPA Intramural Federal Research

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:

This modification, dated July 8, 2008, allows researchers to start the third exposure before all 6 participants have completed the second exposure. No effects were observed from the first two exposures.

Investigator's Responsibilities:

When applicable, enclosed are stamped copies of approved consent documents and other recruitment materials. You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
James Samet, Environmentally Protection Agency
Robert Truckner, (EPA), Non-IRB Review Contact

Wanda Simmons, (GCRC), Non-IRB Review Contact